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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,059	02/28/2002	Georg Baljer	20740-242738	4352

25764 7590 12/17/2004

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,059	BALJER ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *01 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5 and 17-34* is/are pending in the application.

4a) Of the above claim(s) *17-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

1. Acknowledgment and entry of the Amendment submitted on 10/1/04 is made. Claims 1, 3, 5 and 32-34 are currently under examination.

Claims 6-16 are cancelled. Claims 17-31 were previously withdrawn because they are drawn to a non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 3, 5 and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it recites a terminal histidine tag with no size limitation. It is unclear if the his tag can be as small as one histidine in length. It does not appear that such a small size would add anything to the already well known 2e Shiga toxin B subunit. The confusion of size with respect to the terminal histidine tag is compounded by the fact that the specification on page 2, last paragraph, recites that the His tag preferably comprises six histidines which is about 0.66kDa in size.

Claim 5 is vague and indefinite because it is unclear how the recombinant fusion proteins has "a plurality of crosslinked fusion proteins". This is unclear. What does this mean? Is this a huge protein cluster of various recombinant proteins? Applicants did not respond to this rejection in their most recent reply. Clarification is requested.

Claim 33 is vague and indefinite because it is unclear whether the 'fusion protein' recited is in reference to the 2e Shiga toxin B subunit fused to the terminal His tag or if an additional heterologous polypeptide is intended. Clarification is requested.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 3, 5 and 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Carroll et al (WO 96/30043).

Carroll et al teach a B subunit of the 2e Shiga toxin which is produced by *E.coli* with a histidine terminal tag. The bottom of page 23 recites that the amino acid sequence of the histidines tagged 2e Shiga toxin B subunit (VT-2 B subunit) is listed in SEQ ID NO:27 and the VT-1 B subunit is listed in SEQ ID NO:23. SEQ ID NO:11 provides the sequence of the C-terminal extension which includes 6 His residues. See also first full paragraph of page 44. See page 13, lines 13-31 which describe the poly-histidine tag. It is recited that six to ten residues is preferred. Lines 13-20 recite that the his tag may be a fusion protein with the 2e Shiga toxin fragment. It is taught that the

histidine tag facilitates the purification of a recombinant fusion protein from a host cell, host cell culture supernatant, or both. Chimeric proteins are also taught in the paragraph bridging pages 13-14. These may include a plurality of different cross-linked proteins. The references teaches that these compositions may be used in the treatment of human or animals. Additionally, the term "pharmaceutical" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The claimed pharmaceutical compositions solely comprise the recombinant fusion protein comprising a B subunit of the 2e Shiga toxin in fusion with a terminal histidines tag and are, therefore, anticipated by Carroll et al.

Verotoxin is a shiga-like toxin which is produced by *E.coli* and is known in the art to be a member of the Stx2 Group. Shiga toxin 2e (St2xe) is produced by host-adapted Shiga toxin-producing *E.coli* strains (STEC) and causes edema disease in weaned pigs. This toxin is the same as the verotoxin-2 disclosed by Carroll et al.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3, 5 and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Franke et al (Vet Microbiol. 1995. 43: 41-52), Acheson et al. (Infect. Immun. 1995. 63(1) : 301-8) or Wieler et al (Lecture read at the 21st DVG congress at Bad Nauheim March 1995) in view of Carroll et al (WO 96/30043).

Franke et al teach a recombinant fusion protein comprising the B subunit of Stx2e and GST (glutathion S transferase) as the terminal tag. Franke teach that the recombinant SLT-II B subunit may be a possible candidate for a vaccine. Acheson et al teach that the B subunit of the Stx2e toxin can induce the formation of toxin-neutralizing antibodies after parental application. The Stx2e was expressed as a fusion protein with maltose binding protein. Weile teach that the recombinant fusion protein from a fragment of the Stx2eb subunit and the Glutathion S transferase was used to monitor the antibody response of an outbreak of edema disease in piglets. The reference teaches that the fusion protein is good candidate for a potential vaccine.

However, Franke, Acheson and Weiler do not particularly exemplify a fusion protein which comprises the Stx2e B subunit with a His tag, or more preferably a His_6 tag.

The teachings of Carroll are set forth above. Carroll et al teaches fusions with solely the B subunit of the verotoxin-1 or verotoxin-2 (Stx2e) and a histidine tag. Carroll teaches that the his terminal tag greatly facilitates purification of the toxin subunits. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute any of the terminal tags taught by Franke, Acheson and Weiler with the his tag taught by Carroll because it would be expected to work equally as well as the

the his tag taught by Carroll because it would be expected to work equally as well as the GST or MBP tags taught by the prior art references when used for purification and one of ordinary skill in the art would be especially motivated to substitute this tag for the tags taught by the primary prior art references when using it as an immunogen as is contemplated in said references because the his tag would not be expected to cause interfering and detrimental immune responses when administered to a host *in vivo*.

Prior art not relied on:

8. O'Brien et al (WO 98/11229, March 19, 1998).

O'Brien et al disclose histidine-tagged shiga toxin fusion proteins. O'Brien et al teach that histidine tagging greatly facilitates purification of Shiga toxins. The use of the histidine-tagged fusion proteins for generating an immune response against infection or transmission by bacteria expressing Shiga toxin is also taught. See page 1, lines 15-21. O'Brien teach that Shiga toxin includes any toxin in the Stx1 or Stx2 group. See page 3, lines 9-10. Stx2e is specifically taught as a member of the Stx2 group. See page 3, lines 1-5. O'Brien et al teach that smaller fragments of the Shiga toxin tagged to His may be used. See page 6, lines 16-29. The reference teaches that a smaller fragment might may be selected to enhance stability of the combined fusion protein. Page 17, lines 18-29 teach that various proteins, haptens and antigens from bacteria, rickettsiae, fungi and parasites may be added to the fusion protein. The use of adjuvants are taught. However, the reference does not teach solely the Stx2e B subunit (it teaches both the A and B subunits together) and a His_6 tag.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action, *e.g., a His terminal tag was not recited in the previous claims.* Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

Jennifer Graser
Primary Examiner
Art Unit 1645

12/15/04